

# Role of Enteral Immunonutrition in Patients with Gastric Carcinoma Undergoing Major Surgery

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**OBJECTIVE:** To evaluate the influence of postoperative immunonutrition on immune and nutritional parameters in patients with gastric carcinoma.

**METHODS:** From September 2002 to August 2003, 40 patients with gastric carcinoma who had undergone major surgery were randomly divided into an immunonutrition group and standard nutrition group, each of 20 patients. On postoperative Day 2, patients in the standard nutrition group received a standard enteral formula, while those in the immunonutrition group received an enteral formula enriched with glutamine, arginine and omega-3 fatty acids. Nutritional support was continued for 7 days. Blood samples were obtained to determine plasma albumin, prealbumin and transferrin on Days 0, 5 and 9. On Days 0, 1 and 9, blood samples were collected to detect immunoglobulin (Ig) A, IgG, IgM, CD4 and CD8 cell counts, the ratio of CD4/CD8, interleukin (IL)-2, IL-6 and tumour necrosis factor (TNF)- $\alpha$ , respectively.

**RESULTS:** There were no significant differences between the two groups in protein and immune parameters preoperatively and no significant differences in management perioperatively. No serious adverse effects were recorded with the two formulas. Postoperative procedures were smooth in both groups. On Day 9, serum levels of prealbumin and transferrin were higher in the immunonutrition group than in the standard nutrition group ( $p < 0.01$ ). After 7 days' nutritional support, patients in the immunonutrition group had higher levels of immunoglobulin, CD4 cell counts, CD4/CD8 ratio and IL-2 than those in the control group, whereas IL-6 and TNF- $\alpha$  levels were significantly lower in the immunonutrition group.

**CONCLUSION:** Compared with standard enteral nutrition, enteral immunonutrition can improve defence mechanisms and modulate inflammatory action after major elective surgery for gastric carcinoma. [*Asian J Surg* 2005;28(2):121-4]

**Key Words:** gastric carcinoma, immunonutrition, inflammatory

## Introduction

In patients receiving nutritional support, the delivery of nutrients via the enteral route is more effective and economical than via the parenteral route.<sup>1-3</sup> During recent years, many investigations of enteral nutrition have focused on the ability to modulate the immune response to injury via specially formulated enteral diets enriched with arginine, glutamine and

omega-3 fatty acids.<sup>4-7</sup> Enteral immunonutrition is standard-formula enteral nutrition supplemented with specific compounds, such as arginine, glutamine, omega-3 fatty acids and RNA, which have particular ability to improve immune defensive and intestinal barrier function and to modulate the inflammatory response.<sup>8-10</sup> Currently, one enteral immunonutritional product is available for clinical use in China. It contains high-dose glutamine, arginine and omega-3 fatty

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acids, which enhance the effect of nutritional support.

We designed a prospective randomized clinical trial to test whether enteral immunonutrition improved defence mechanisms and modulated inflammatory action after major surgery compared with standard enteral nutrition.

## Patients and methods

From September 2002 to August 2003, 40 patients undergoing major elective surgery for gastric carcinoma were included in this study. There were 28 males and 12 females with a mean age of  $59.03 \pm 12.55$  years (range, 31–75 years). The protocol was approved by the ethics committee of our hospital. All patients were required to sign a written informed consent form before entering the trial. Patients were excluded from the study if they had previously had radiotherapy or treatment with immunosuppressive drugs or had AIDS, endocrine or metabolic disorders, any known allergic disease, sepsis, pre-existing severe chronic disease or congestive heart failure. The patients were randomly divided into an immunonutrition group and a standard nutrition group, each of 20 patients. Those in the immunonutrition group received an enteral immunonutrition product enriched with arginine, glutamine and omega-3 fatty acids (Stresson®, Nutricia China, Shanghai, China), while the standard nutrition group received standard enteral nutrition (Nutrison®; Nutricia China) (Table 1).

Enteral nutrition was administered by nasoenteric tube. The enteral feeding tube was inserted through a nostril and advanced by the surgeon to 10 cm beyond the jejunojejunal or

gastrojejunal anastomosis during the operation. On postoperative Day 2, patients received 25% of the planned caloric goal, based on 30 non-protein calories/kg/day. On postoperative Day 3, 50% of the planned caloric goal was given. From postoperative Day 4 until the end of the study, patients received 100% of the planned caloric goal. There were no differences in preoperative clinical profiles of patients and postoperative management between the two groups, except the formula of enteral nutrition, which was similar apart from the three specific nutrients mentioned above.

In both groups, peripheral venous blood was collected to determine plasma levels of albumin, transferrin and prealbumin on postoperative Days 0, 5 and 9. Another blood sample was obtained on postoperative Days 0, 1 and 9 to detect immunoglobulin (Ig) A, IgG, IgM, CD4 and CD8 cell counts, the ratio of CD4/CD8, interleukin (IL)-2, IL-6 and tumour necrosis factor (TNF)- $\alpha$ .

## Results

The two formulas were tolerated well and the postoperative process was uneventful. No intestinal fistula, respiratory failure or liver dysfunction developed after surgery. The regimens did not influence complication frequency or clinical recovery.

The serum albumin level did not change significantly during the postoperative period, and no difference was observed between the two groups (Table 2). A significant difference in prealbumin and transferrin levels was found between the two groups on Day 9. Although the pattern of change was the same in both groups, the levels of prealbumin and transferrin in the experimental group were higher than those in the control group.

**Table 1.** Main differences in composition of two nutritional formulas (per L)

	Stresson®	Nutrison®
Total energy (kcal)	1,250	1,000
Total protein (g)	75.0 (24 EN%)	40.0 (16 EN%)
Arginine (g)	8.9	1.6
Glutamine (g)	13.0	4.0
Fats (g)	4.17 (30 EN%)	3.89 (35 EN%)
Long-chain fatty acids (g)	24.5	38.9
Medium-chain fatty acids (g)	17.2	0
Omega-6:omega-3 fatty acids	3.45:1	5:1
Carbohydrates (g)	145 (46 EN%)	123 (49 EN%)
Fibre (g)	9	50
Vitamin E (mg)	49.2	8.1
Osmolarity (mOsm/L)	380	250

EN% = percentage of total energy.

**Table 2.** Variations in serum proteins

	Albumin (g/L)	Prealbumin (mg/L)	Transferrin (mg/L)
Stresson®			
Day 0	36.15 $\pm$ 3.60	197.9 $\pm$ 24.05	2.41 $\pm$ 0.56
Day 5	33.75 $\pm$ 3.39	148.5 $\pm$ 22.22	1.85 $\pm$ 0.43
Day 9	36.05 $\pm$ 2.95	194.0 $\pm$ 39.82	2.07 $\pm$ 0.52
Control			
Day 0	36.80 $\pm$ 4.76	187.2 $\pm$ 51.79	2.15 $\pm$ 0.54
Day 5	33.30 $\pm$ 4.05	142.6 $\pm$ 38.50	1.51 $\pm$ 0.34
Day 9	35.26 $\pm$ 2.96	162.5 $\pm$ 45.73*	1.60 $\pm$ 0.42 <sup>†</sup>

\* $p < 0.05$ , <sup>†</sup> $p < 0.01$  compared with control group.

Plasma immunoglobulin concentrations, CD4 and CD8 cell counts and cytokine concentrations were comparable in the two groups preoperatively. However, on Day 9, serum immunoglobulin level, CD4 cell counts, CD4/CD8 ratio and IL-2 were higher in the immunonutrition group than in the control group, whereas IL-6 and TNF- $\alpha$  levels were significantly lower in the immunonutrition group (Table 3). These results indicate that immunonutrition can increase immunity and modify the inflammation triggered by surgical intervention.

## Discussion

Surgical intervention usually results in further impairment of immune defence mechanisms and altered inflammatory responses in patients who have underlying disorders of nutritional and immune function.<sup>11-13</sup> Evidence increasingly shows that nutritional support reduces postoperative complications and improves surgical outcomes.<sup>14,15</sup> The most rational approach may be enteral immunonutrition support. Some investigations show that enteral immunonutrition has pharmacological effects on immune and inflammatory functions.<sup>4,5,16</sup> Compared with the standard nutritional formula, Stresson® contains enriched arginine (8.9 g/L), glutamine (13 g/L) and an appropriate ratio of omega-6/omega-3 fatty acids, which are involved in all aspects of the immune system.

Glutamine is a major and favourite fuel for lymphocytes and macrophages. It is a precursor for nucleotide synthesis and acts as a precursor for glutathione, a major link in the antioxidative defence system. Lymphocytes have high glutaminase activity and high glutamine utilization, both of which increase after a mitogenic stimulus.<sup>8,17,18</sup> Thus, lymphocyte

function would be affected by glutamine deficiency. *In vitro* experiments show that glutamine is required for increased phagocytosis, RNA production and IL-1 secretion by macrophages.<sup>19</sup> Polymorphonuclear cells after burn injury also appear to have more effective bactericidal function in the presence of glutamine.<sup>20</sup>

Arginine stimulates secretion of a variety of hormones, such as growth hormone, glucagons and insulin, each of which has profound modulatory effects on immune response.<sup>21</sup> It is a precursor for synthesis of polyamines and nucleic acids, both of which are indispensable substances for cell proliferation and differentiation.<sup>22</sup> Furthermore, arginine is a direct precursor of nitrogen oxide and some of its function is mediated by the L-arginine-nitric oxide pathway.<sup>9</sup> Arginine also increases lymphocyte mitogenic and allogenic responses and natural killer cell cytotoxicity. It can enhance IL-2 production and receptor activity, which are involved in reprioritization of protein synthesis.<sup>23</sup>

The role fatty acids play in modulating the immune response is based on their effects on the structural and functional integrity of the cell membrane, intercellular signal transduction and synthesis of the eicosanoids (important immune mediators).<sup>10</sup> By replacing other fatty acids with omega-3 fatty acids, membrane flexibility is enhanced, which is essential for phagocytosis and expression of IL-2 receptors.<sup>24</sup> *In vivo* experiments have shown that omega-3 fatty acids reduce IL-1, IL-2, IL-6 and TNF production by peripheral monocytes.<sup>25</sup> In contrast to these immune-enhancing effects, omega-3 fatty acids used for eicosanoid synthesis are immunologically less potent mediators than their omega-6 counterparts.<sup>10</sup>

Inflammation is essential for healing, immune processes and successful recovery after injury. However, uncontrolled

**Table 3.** Variations in immune and inflammatory factors

	Experimental group			Control group		
	Day 0	Day 1	Day 9	Day 0	Day 1	Day 9
IgA (g/L)	2.33 $\pm$ 0.81	1.90 $\pm$ 0.54	3.04 $\pm$ 0.48	2.44 $\pm$ 1.01	1.95 $\pm$ 0.88	2.54 $\pm$ 0.91*
IgG (g/L)	10.53 $\pm$ 1.39	9.20 $\pm$ 1.16	13.22 $\pm$ 1.34	10.76 $\pm$ 1.40	9.17 $\pm$ 1.15	12.18 $\pm$ 1.29*
IgM (g/L)	1.42 $\pm$ 0.29	1.07 $\pm$ 0.44	1.71 $\pm$ 0.42	1.39 $\pm$ 0.24	0.95 $\pm$ 0.43	1.45 $\pm$ 0.40*
CD4	41.07 $\pm$ 13.75	33.56 $\pm$ 6.02	48.04 $\pm$ 6.71	41.19 $\pm$ 8.78	32.86 $\pm$ 8.40	40.37 $\pm$ 7.21†
CD8	24.88 $\pm$ 3.67	23.15 $\pm$ 7.95	21.68 $\pm$ 8.54	25.15 $\pm$ 6.63	23.55 $\pm$ 6.72	23.29 $\pm$ 4.04
CD4/CD8	1.67 $\pm$ 0.56	1.57 $\pm$ 0.52	2.92 $\pm$ 2.49	1.72 $\pm$ 0.44	1.51 $\pm$ 0.58	1.77 $\pm$ 0.37*
IL-2 (pg/mL)	284.21 $\pm$ 73.89	290.34 $\pm$ 74.96	368.56 $\pm$ 65.15	257.22 $\pm$ 58.22	280.34 $\pm$ 49.21	317.70 $\pm$ 48.71†
IL-6 (pg/mL)	268.68 $\pm$ 108.50	537.01 $\pm$ 107.26	411.13 $\pm$ 124.79	299.22 $\pm$ 128.69	584.01 $\pm$ 161.11	519.33 $\pm$ 122.89†
TNF- $\alpha$ (pg/mL)	280.22 $\pm$ 44.41	373.58 $\pm$ 120.61	320.59 $\pm$ 83.44	284.27 $\pm$ 45.46	386.05 $\pm$ 118.02	439.74 $\pm$ 98.17†

\* $p$  < 0.05, † $p$  < 0.01 compared with experimental group. Ig = immunoglobulin; IL = interleukin; TNF = tumour necrosis factor.

systemic inflammatory responses lead to organ dysfunction and adverse outcome.<sup>26</sup> Further, it has been suggested that injury alters the balance of protein synthesis by switching from constitutive to acute-phase proteins through the release of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6.<sup>27</sup> This may be associated with a rapid decrease in nitrogen balance, with loss of lean body mass and with catabolic response.

In our study, we observed that immunonutritional support increased serum immunoglobulin levels and enhanced the levels of CD4 cells and the CD4/CD8 ratio compared with standard enteral nutrition. We also found that immunonutritional support successfully increased the serum level of IL-2 and decreased the serum level of IL-6 and TNF- $\alpha$ . The positive effect of immunonutrition on immunity and inflammation is due to its high doses of glutamine, arginine and omega-3 fatty acids, which greatly affect non-specific and specific immunity.

## Conclusion

Our results demonstrate that immunonutrition is superior to standard nutrition in restoring immunity and modulating inflammatory reaction in patients who have undergone major surgery, which implies that enteral immunonutrition may be a promising form of nutritional support.

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